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EXAMINER	
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1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,038	CARLONE ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,6,7,12 and 12-23* is/are pending in the application.

4a) Of the above claim(s) *7,13,14,17,19,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,6,12,15,16,18,20 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence report (1)*.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 01/27/05 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 01/27/05 in response to the final Office Action mailed 07/23/04.

Status of Claims

3) Claims 1, 3-5 and 8-11 have been canceled via the amendment filed 01/27/05.

Claims 2, 6, 12, 15 and 20 have been amended via the amendment filed 01/27/05.

New claim 23 has been added via the amendment filed 01/27/05.

Claims 2, 6, 7 and 12-23 are pending.

Claims 2, 6, 12, 15, 16, 18, 20 and 23 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to claims 6, 12, 15 and 20 made in paragraph 20 of the Office Action mailed 08/27/03 and maintained in paragraph 9 of the Office Action mailed 07/23/04 is withdrawn in light of Applicants' amendment to the claims.

Rejection(s) Moot

7) The provisional rejection of claims 1 and 3-5 made in paragraph 16 of the Office Action mailed 08/27/03 and maintained in paragraph 20 of the Office Action mailed 07/23/04 under the judicially created doctrine of obviousness-type double patenting over claims 1, 2, 8 and 12-14 of the co-pending application SN 09/613,092, is moot in light of Applicants' cancellation of the claims.

8) The provisional rejection of claims 1, 3-5 and 8-11 made in paragraph 18 of the Office Action mailed 08/27/03 and maintained in paragraph 23 of the Office Action mailed 07/23/04 under 35 U.S.C § 102(e) as being anticipated by Sampson *et al.* (US 6,217,884), is moot in light of Applicants' cancellation of the claims.

9) The rejection of claim 1 made in paragraph 19 of the Office Action mailed 08/27/03 and maintained in paragraph 24 of the Office Action mailed 07/23/04 under 35 U.S.C § 102(b) as being anticipated by Nuijens *et al.* (WO 9117258) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988), is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

10) The provisional rejection of claims 2, 6, 12, 15, 16, 18 and 20 made in paragraph 16 of the Office Action mailed 08/27/03 and maintained in paragraph 20 of the Office Action mailed 07/23/04 under the judicially created doctrine of obviousness-type double patenting over claims 1, 2, 8 and 12-14 of the co-pending application SN 09/613,092, is withdrawn in light of the cancellation of claims 1, 2, 8 and 12-14 of the co-pending application SN 09/613,092.

11) The rejection of claims 12, 15, 16, 18 and 20 made in paragraph 14 of the Office Action mailed 08/27/03 and maintained in paragraph 22 of the Office Action mailed 07/23/04 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicants' amendments to the claims. A new rejection is set forth below to reject the claims, as amended.

12) The rejection of claim 15 made in paragraph 19 of the Office Action mailed 08/27/03 and maintained in paragraph 24 of the Office Action mailed 07/23/04 under 35 U.S.C § 102(b) as being anticipated by Nuijens *et al.* (WO 9117258) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A*

Laboratory Manual. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988), is withdrawn in light of Applicants' amendment to the claim deleting the limitation 'immunogenic fragment'.

13) The rejection of claim 6 made in paragraph 19 of the Office Action mailed 08/27/03 and maintained in paragraph 24 of the Office Action mailed 07/23/04 under 35 U.S.C § 102(b) as being anticipated by Nuijens *et al.* (WO 91/17258) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988), is withdrawn in light of Applicants' amendment to the claim. A new art rejection is made below to reject claim 6, as amended.

Rejection(s) Maintained

14) The rejection of claim 2 made in paragraph 12 of the Office Action mailed 08/27/03 and maintained in paragraph 20 of the Office Action mailed 07/23/04 under 35 U.S.C. § 112, first paragraph, with regard to the deposit issue, is still maintained for reasons set forth therein and herebelow.

Applicants state that claim 2 has been amended to refer to an ATCC deposit of the monoclonal antibody, 1B6E12H9. Applicants contend that the antibody is shown in Table 4 to bind to SEQ ID NO: 6. Applicants state that a deposit number has not yet been provided by ATCC and therefore it is not included in the claim. Applicants assure the Office that the claim and the specification will be amended to insert the deposit number and the required depository information when the deposit number becomes available.

Applicants' arguments have been carefully considered. The rejection would be maintained until Applicants comply with the deposit issues.

15) The provisional rejection of claim 2 made in paragraph 18 of the Office Action mailed 08/27/03 and maintained in paragraph 23 of the Office Action mailed 07/23/04 under 35 U.S.C § 102(e) as being anticipated by Sampson *et al.* (US 6,217,884), is maintained for reasons set forth therein and herebelow.

Applicants submit that claim 2 recites a purified peptide that immunospecifically binds a specific monoclonal antibody. Applicants state that the monoclonal antibody 1B6E12H9 is *not* disclosed in the '884 patent.

Applicants' argument has been carefully considered, but is not persuasive. The statement

that the monoclonal antibody 1B6E12H9 is not disclosed in the '884 patent is *incorrect*. Contrary to Applicants' assertion, the '884 patent explicitly discloses a monoclonal antibody designated '1B6E12H9' (see last paragraph in column 12), the same monoclonal antibody recited in the instant claim 2. The rejection stands.

Applicants' Arguments on Lack of Enablement (Scope)

16) (a) Applicants' submit that claim 12 has been amended to delete reference to 'fragments', yet continue to argue that the peptide be protective means that the fragment must be at least 6 amino acids in length.

Applicants' arguments are moot in light of the deletion of the limitation 'immunogenic fragment of SEQ ID NO: 6' from claim 12. The lack of enablement analysis is still applicable to the peptides of SEQ ID NO: 6 having the ability to 'confer protective immunity against *S. pneumoniae* infection when administered to a subject', because there is no evidence of record showing that a composition comprising one or more peptides comprising the 15 amino acid-long amino acid sequence of SEQ ID NO: 6 does in fact serve as a 'therapeutic' composition and confers protective immunity against *S. pneumoniae* infection when administered to a subject. See paragraph 22 below for a detailed analysis.

(b) Applicants' submit that claim 15 has been amended to recite '90% identical to the peptide of SEQ ID NO: 6'. Applicants state that the number of peptide variants of SEQ ID NO: 6 with 90% similarity is only 300, a small number that can be routinely made and tested, given the amount of experimentation viewed as routine in this art. Applicants submit lengthy arguments, which revolve around the statement that 'claim 15 requires that the peptide be immunogenic' and no more.

In response, Applicants' statement that 'claim 15 requires that the peptide be immunogenic' is *erroneous*. As presented currently, the product of claim 15 is not associated with any function. For the record, claim 15, as amended currently, is reproduced here below:

> 15. (currently amended) A purified peptide comprising an amino acid sequence which is at least ~~80%~~ 90% identical to ~~a~~ the peptide ~~whose sequence is chosen from the group consisting of SEQ ID NO: 5 or an immunogenic fragment thereof~~, of SEQ ID NO: 6 ~~or an immunogenic fragment thereof, SEQ ID NO: 7 or an immunogenic fragment thereof, and SEQ ID NO: 8 or an immunoegnic fragment thereof~~.

All of Applicants' arguments with respect to the peptide of claim 15 not being immunogenic

have been considered, but are moot since the peptide of the amended claim 15 is *not* recited to be 'immunogenic'.

(c) On page 14 of the amendment/response filed 01/27/05, Applicants make the following statements:

> Incidentally; applicants note that *S. pneumoniae* specificity is not recited in the claim 15. In fact, the peptides listed in claim 15 are **not PsaA peptides**, but were identified in phage display of random peptides. What is clear is that SEQ ID NO: 6 immunospecifically binds a monoclonal antibody that doesn't bind naturally occurring proteins other than PsaA. Thus it mimics an epitope specific for the PsaA protein of *S. pneumoniae*. [Emphasis added]

In response, it should be noted that although the at least 90% identical peptide variants of claim 15 are not recited as being *S. pneumoniae*-specific and protective against *S. pneumoniae* infection, the compositions of the two claims, claims 16 and 18 that depend from claim 15, are required to confer protective immunity against *S. pneumoniae* infection when administered to a subject. It is common sense that if the peptide variant is not *S. pneumoniae*-specific, it would not bind immunospecifically to the pneumococcal pathogens and would not confer 'protective immunity against *S. pneumoniae* infection when administered to a subject'. One example of a peptide encompassed in claim 15 is a purified peptide having 100% identity to the peptide of SEQ ID NO: 6: RSYQHDLRAYGFWRL. Structure-wise, this peptide is necessarily a PsaA peptide, no matter whether it is obtained by fragmentation of the full-length PsaA, produced synthetically, or identified in the phage display of random peptides. Therefore, Applicants' statement that 'the peptides listed in claim 15 are not PsaA peptides' makes no sense.

(d) With regard to the composition comprising the peptide of SEQ ID NO: 6, Applicants submit the post-filing reference of Johnson *et al.* (*J. Clin. Infect. Dis.* 185: 489-496, 2002) and state that the composition has been shown to reduce nasopharyngeal carriage of *S. pneumoniae*. This reference is stated as showing that immunization with composition 'P79' containing SEQ ID NO: 6/P2 reduced the nasopharyngeal carriage of *S. pneumoniae* in mice. Applicants conclude that: (i) there is thus evidence in the literature that confirms the protective immunogenic effect of 'peptides comprising SEQ ID NO: 6'; and (ii) the process of modifying a single amino acid in the 15-mer peptide of SEQ ID NO: 6 and testing it for protective immunogenicity is well within the skill in the art as evidenced by Johnson *et al.*

In response, the post-filing reference of Johnson *et al.* (2002) shows that a MAP or bipeptide

P79 consisting of *two* units each of base peptides P1 (T-V-S-R-V-P-W-T-A-W-A-F-H-G-Y) and P2 (R-S-Y-Q-H-D-L-R-A-Y-G-F-W-R-L) reduced the nasopharyngeal carriage of *S. pneumoniae* in mice immunized with the MAP or bipeptide. See Figure 3 legend; page 491; and Table 3. What reduced the nasopharyngeal carriage of *S. pneumoniae* in Johnson's study is a bipeptide or MAP that additionally comprised the P1 peptide (T-V-S-R-V-P-W-T-A-W-A-F-H-G-Y). What is being claimed in the instant claims 16, 18, 20 and 12 is not the MAP or the P79 bipeptide comprising the peptide of SEQ ID NO: 6 **plus** the P1 peptide, T-V-S-R-V-P-W-T-A-W-A-F-H-G-Y, but one or more peptides comprising the amino acid sequence of SEQ ID NO: 6, or a therapeutic composition comprising one or more peptides each comprising the amino acid sequence of SEQ ID NO: 6, or a therapeutic composition comprising a peptide that is at least 90% identical to the peptide of SEQ ID NO: 6, wherein the therapeutic composition 'confers protective immunity against *S. pneumoniae* infection when administered to a subject'. A therapeutic composition comprising the peptide(s) of SEQ ID NO: 6 alone or its 90% identical variant thereof, in the absence of the P1 peptide, is not enabled within the instant specification, or within the post-filing reference of Johnson *et al.* (2002).

The protective ability of a 15 amino acid-long peptide such as SEQ ID NO: 6, or a 90% identical variant thereof is neither demonstrated, not predictable. The disclosure in the instant specification is limited to a showing that the 15 amino acid-long peptide of SEQ ID NO: 6 containing an antigenic epitope, but not a 'protective' epitope which 'confers protective immunity against *S. pneumoniae* infection when administered to a subject'. Applicants' assertions that the unpredictability of protection is balanced by the routine nature, and that a small amount of research required to test SEQ ID NO: 6 for protective effect, are unsubstantiated. Despite the high level of skill in the art, a plethora of publications at the time of the invention disclosed the difficulty in making such a prediction. Because the invention is in an art that is unpredictable, the quantity of experimentation needed is extensive and undue. See paragraph 22 below. Even if one tests SEQ ID NO: 6 and several of its at least 90% identical variants for protective effect, there is absolutely no predictability that the peptide and its variants would retain the protective ability of the native PsaA against *S. pneumoniae* infection. Applicants are simply incorrect in their statement that only peptides that comprise SEQ ID NO: 6 need to be assayed, because the peptide variants of claims 16 and 18 also need to be assayed in the face of the art-recognized unpredictability. In applications

directed to inventions in arts where the results are unpredictable, the disclosure of a single immunogenic peptide species usually does not provide an adequate basis to support generic claims encompassing protective peptides and peptide variants. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). In the instant case, there is no protective data even for the unmodified peptide of SEQ ID NO: 6, let alone its variants. This is because it is not obvious from the disclosure of one species, what other species will work. In the instant application, the only product that has been enabled as a protective immunogen is the 37 kDa PsaA protein.

(e) On page 16 of the amendment/response filed 01/27/05, Applicants make the following statements:

> Under a Wands analysis, the unpredictability of protection is fully balanced by the routine nature and small amount of research required to test SEQ ID NO: 6 for protective effect. Applicants do not believe that the Office is asserting that the nature of this type of test is other than routine. This combined with the fact that only peptides that comprise SEQ ID NO: 6 need to be assayed, contradicts any assertion that undue experimentation would be required to practice the invention of claim 12. To the extent that the Office maintains this rejection, it would appear that it is applying a per se requirement for efficacy data, a position which is not supported in the law.

Applicants further allege that the Office has given disproportionate weight to predictability and is creating a requirement for more data than the law actually requires. Applicants assert that despite the focus on predictability and data, the present case has an equivalent amount of data. Applicants allege that there is no factual basis provided in the Office Action as to why the work required to practice the invention would be considered undue by one in this field. Applicants further allege that the Office has ignored Applicants' previous assertions regarding the routine nature and amount of work required to practice the invention. Applicants further state that they can understand why it is difficult for the Office to find any factual basis to conclude that this work is more than routine because of the frequency with which this type of work is done by those in the art. Applicants cite Barany *et al.* (198) and Tam *et al.* (1989) and state that the routine nature of making and testing peptides for antigenicity and immunogenicity is found in these references.

In response, the law with regard to the unpredictability factor is clear. The predictability or unpredictability is a *Wands* factor, which cannot be dismissed in the face of what is evident from the state of the art on amino acid variation in a peptide. MPEP 2164.03 [R-2] sets forth the relationship of predictability of the art and the enablement requirement. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated: [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.] In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species

usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In the instant case, the only product that is shown to be protective against *S. pneumoniae* infection is the purified 37 kDa PsaA protein. One skilled in the art cannot extrapolate these results disclosed for the full length 37 kDa protein to the claimed peptide of SEQ ID NO: 6, or to its at least 90% identical variants (see also paragraph 22 below). Thus, the case law pertaining to unpredictability actually requires something more concrete than the mere allegation that the Office has given disproportionate weight to predictability. Barany *et al.* (198) and Tam *et al.* (1989) do not teach how to make peptide variants that retain the protective ability of the native full length protein.

Contrary to Applicants' allegation, the Office did provide the solid scientific reasoning as to why the work required to practice the invention would be considered undue by those skilled in this field. The Office supported the rejection by citing the teachings of Houghten *et el.* which Applicants have fully ignored. Applicants have failed to advance any arguments with regard to the cited teachings of Houghten *et el.* In view of the overly broad scope of the claims, the Office's focus on unpredictability and lack of enabling protective data, even for the unmodified peptide of SEQ ID NO: 6, is fully justified under the provisions of 35 U.S.C. 112, first paragraph. Applicants have not identified within the instant specification what they characterize as 'equivalent data' in connection with protection. The standard to be met under 35 U.S.C. 112, first paragraph, is not mere 'experimentation', but 'undue experimentation' in the face of the art-recognized functional unpredictability. The predictability of amount and nature of the 'analysis' is not a *Wands* factor. Contrary to Applicants' assertion, predictability of outcome is required to practice the invention since the art indicates that even a single amino acid variation can drastically change the biologic functions and the immunospecificity of the peptide. A 90% identical peptide variant of SEQ ID NO: 6 may be predictably immunogenic, but the *S. pneumoniae*-specific immunogenicity of such a

variant is neither established, nor unpredictable. See paragraph 22 below for a detailed analysis. In order to be of specific use in the instant invention for the intended prophylactic, therapeutic and/or diagnostic purposes, and irrespective of whether or not identified in phage display of random peptides, the peptide claimed in claim 15 is *required* to be at least *S. pneumoniae*-specific even though the claim does not so recite. Otherwise, Applicants are not claiming what they invented, but are claiming a peptide variant that has no specific utility in the claimed invention. Furthermore, it is important to note that the state of the art reflects functional unpredictability with regard to even conservative amino acid substitutions. For instance, Lazar *et al.* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) demonstrated that a substitution of Leu with a conservative amino acid residue, such as, Ile or His, in the transforming growth factor (TGF) alpha led to a mutant protein with dramatically altered biological activities. Lazar *et al.* stated that they 'did not expect that a mutation of Leu to Ile (which have similar sizes and polarities) would cause such a strong effect'. See paragraph bridging left and right columns on page 1251; and third full paragraph on page 1251. Applicants assert that one of skill in the art would be able to make a single amino acid variation in SEQ ID NO: 6 by routine experimentation. However, Applicants have failed to show that such a single amino acid variation in the peptide of SEQ ID NO: 6 would result in a peptide variant that would retain the functional and biologic integrity (i.e., the protective ability) of the 37 kDa PsaA protein and can be used for protective purposes in a therapeutic composition.

(f) With regard to the product claimed in claims 16 and 18, Applicants contend that in the context of providing a credible basis for a protective effect, enablement of these claims has the same basis as the enablement of claim 12. Applicants state that they have shown how the scope of claims covering at least 90% similar variants are enabled due to the routine amount and nature of the work required to practice the full scope of the invention, and conclude that this applies to claims 16 and 18, because they have this scope. Applicants assert that they have also shown how the protective aspect of the claimed peptides is routinely established. Applicants again point to the post-filing reference of Johnson *et al.* (2002) and state that the process of modifying a single amino acid in the 15-mer peptide and testing it for protective immunogenicity is well within the skill in the art as evidenced by the study done in Johnson *et al.* (2002).

With regard to the Office's rejection of claim 20, Applicants contend that there is no

recitation of sequence variants in claim 20. Applicants allege that the Office Action does not substantively address the issue of the nature of the invention, state of the prior art, quantity of the experimentation necessary to practice the invention. Applicants further allege that the Office's analysis is incomplete, improper and unfairly biased against Applicants.

Applicants' arguments have been carefully considered, but are not persuasive. For reasons fully explained above, in paragraph 22 of the Office Action mailed 07/23/04, and in paragraph 22 below, the rejection under 35 U.S.C 112, first paragraph, is proper, complete and fully justified.

The state of the art has established that the ability of a random peptide of a microbial protein to elicit a species-specific or genus-specific protective immune response in a subject is not predictable. For instance, specifically with regard to a streptococcal Spa peptide, Dale *et al.* (*J. Clin. Investigation* 103: 1261-1268, May 1999) established that a 23 amino acid-long fragment, S-Spa18(1-23)C, having no variation or amino acid substitution, is incapable of providing protection against heterologous Group A streptococci and therefore, against the Group A streptococcal genus. Similarly, Dale (US 6,716,433) showed that the Spa fragment, S-Spa18(1-23)C, 'did not opsonize' type 3 or type 28 group A streptococci, thus indicating the absence of cross-opsonic epitopes in the fragment (see Example 6). This is *prima facie* evidence that one cannot predict a 15 contiguous amino acid-long fragment from PsaA protein, having the amino acid sequence of SEQ ID NO: 6, or a peptide variant thereof having 90% identity to SEQ ID NO: 6, to elicit protective immune response against one or more serotypes of *S. pneumoniae*, or against any specific serotype of *S. pneumoniae*. Applicants are reminded that the Courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001)*. Moreover, the specification must have been enabling at the time the invention was made (see *In re Wright, 27 USPQ2d 1510*). A claim must be enabled over its whole breadth. In this respect, if there are doubts, substantiated by verifiable facts, there is lack of sufficient enablement.

Response to Applicants' Arguments on Nuijens *et al.*

17) Applicants contend that claim 6 is directed to SEQ ID NO: 6 and immunogenic fragments thereof. Applicants state that a peptide must contain an epitope to be immunogenic. Applicants refer to lines 5-7 of page 22 of the instant specification and acknowledge that an immunogenic

fragment must be at least six amino acids in length, because this number of residues is generally viewed in the art of immunochemistry as the minimum length of the epitope. Applicants submit that they have amended claim 6 to recite that the fragment 'has at least six consecutive amino acids of SEQ ID NO: 6'. On page 25 of Applicants' amendment/response filed 01/27/05, Applicants make the following allegations:

> There is **no** six-amino acid region of SEQ ID NO: 6 that is present in the peptide disclosed by Nuijens *et al.* In fact, what the Office Action asserts as the 6-amino acid region of identity (SYQHNL) is **not even identical** in that it contains asparagines (N) in the position where SEQ ID NO: 6 recites asparatic acid (D). Contrary to what is stated in the Office Action, Nuijens *et al.* **do not** disclose SYQHDL. Thus, Nuijens *et al.* discloses, at most, a 4-amino acid region that is identical to a region of SEQ ID NO : 6. This is region is not immunogenic as required by claim 6, because it is not large enough to constitute an epitope. It also does **not** meet the recited size limitation of claim 6. Therefore, it does not anticipate claim 6. [Emphasis in bold added].

Applicants' arguments have been carefully considered, but are not persuasive for the following reasons. Applicants' statement that there is no six-amino acid region of SEQ ID NO: 6 in the peptide disclosed by Nuijens *et al.* is simply inaccurate. Applicants' precise SEQ ID NO: 6 as depicted in the instant Table 4 on page 43 of the instant specification in front of the monoclonal antibody designated '1B6' in Table 4 is reproduced below with the at least 6 consecutive amino acid-containing peptide highlighted:

1B6 R**SYQHDL**RAYGFWRL SEQ ID NO. 6 206-220 (PsaA residue numbers)

The highlighted portion above translates to: -ser-tyr-gln-his-asp-leu, i.e., a peptide from Applicants' SEQ ID NO: 6 which is at least six amino acids in length. The exact same at least 6 consecutive amino acid-containing peptide is taught by Nuijens *et al.* as one of the 'peptide immunogens' under Example II on page 14 of Nuijens *et al.* As depicted at line 3 of page 14 and claims 15 and 17, Nuijens' peptide immunogen comprised the very same peptide: -ser-tyr-gln-his-asp-leu-. Those of skill in the art would understand this peptide as translating to **SYQHDL**, and not to 'SYQHNL' [Emphasis in original] as alleged by Applicants.

Furthermore, it is very important to note that the current allegation or misinterpretation of the Office's rejection of record is quite contrary to Applicants' own previous admission of Nuijens' disclosure. At lines 4-7 of page 47 of their amendment/response filed 12/15/05, Applicants made the following admissive statements:

> Nuijens et al disclose in Example 11 a peptide with the amino acid sequence N-phe-ser-pro-val-**ser-tyr-gln-his-asp-leu**-ala-leu-C. ..... SEQ ID NO; 6 of the present invention is a 15 amino acid peptide: Arg-**Ser-Tyr-Gln-His-Asp-Leu**-Mg-Ala-Tp-Gly-phe-Trp-Arg-Leu. [Emphasis in original].

This is *prima facie* evidence that Applicants' at least six amino acid-containing peptide, **Ser-Tyr-Gln-His-Asp-Leu,** is one and the same as the Nuijens' peptide, **ser-tyr-gln-his-asp-leu,** as readily acknowledged previously by Applicants, and is not the peptide 'SYQHNL' as currently alleged by the same Applicants.

Secondly, although Applicants allege of the Office's assertion of 'SYQHNL' as Nuijens' peptide, Applicants have *failed* to point to a specific portion(s) of the Office Action that so asserted, and/or to a specific portion(s) of the Nuijens reference where one could find Nuijens' teaching of the 'SYQHNL' peptide, as opposed to SYQHDL-containing peptide. Twisting the facts of Nuijens's disclosure does not obviate the rejection of record. In order to establish for the record that the Office correctly identified Nuijens' SYQHDL-containing peptide as anticipating the claimed invention, as opposed to the alleged 'SYQHNL' peptide, the sequence alignment report that was provided to Applicants as an attachment to the Office Action mailed 08/27/03, is reproduced herebelow:

```
RESULT 6
AAR14929
ID   AAR14929 standard; Protein; 12 AA.
XX
AC   AAR14929;
XX
DT   13-FEB-1992  (first entry)
XX
DE   OT-2 antibody binding peptide (2).
XX
KW   Monoclonal antibody; antigen; immunogen; Factor XII; epitope.
XX
OS   Synthetic.
XX
PN   WO9117258-A.
XX
PD   14-NOV-1991.
XX
PF   01-MAY-1991;   91WO-US02990.
XX
PR   10-MAY-1990;   90US-0521820.
XX
PA   (CETU ) CETUS CORP.
XX
PI   Nuijens JH,  Huijbregts CCM,  Hack CE;
XX
DR   WPI; 1991-353779/48.
XX
PT   Treatment of sepsis using inhibitor of factor XII activation -
PT   comprises use of new OT-2 antibody
XX
PS   Claim 15,17; Page 24; 32pp; English.
XX
CC   Based on the known amino acid sequence of Factor XII, peptides
CC   corresp. to neutralising epitopes of the mol. are synthesised and
CC   used as immunogens to produce antibody.  The pref. peptides are
CC   represented in AAR14928-30.  Amino acid Asp in this sequence =
CC   residue 442.
XX
SQ   Sequence   12 AA;

  Query Match           40.0%;  Score 6;  DB 12;  Length 12;
  Best Local Similarity   100.0%;  Pred. No. 4.1;
  Matches    6;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       2 SYQHDL 7
           ||||||
Db       5 SYQHDL 10
```

SEQ ID NO. 6

Double Patenting

18) Claims 12 and 20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claim 11 of the pending application SN 09/613,092. Although the conflicting claims are not identical, they are not patentably distinct from each other because of their overlapping scope with regard to the peptide of SEQ ID NO: 6. The structures of the peptide of SEQ ID NO: 6 disclosed and/or claimed in the two applications are identical (see the attached sequence alignment report). Although claim 11 of the co-pending application does not teach a therapeutic composition comprising the peptide of SEQ ID NO: 6 and an adjuvant or immunostimulatory carrier as recited in the instant claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add an art-known immunostimulatory carrier or an adjuvant to the '092's peptide to produce the therapeutic composition of the instant invention, with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of providing the '092's peptide of SEQ ID NO: 6 beneficially as a therapeutic composition with adjuvant or immune-enhancing properties since such a composition is ideally desired in the art.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

19) Claim 6 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 6, as amended, now includes the new limitation: that has at least six 'consecutive amino acids of SEQ ID NO: 6'. Applicants point to lines 5-7 of page 22 of the specification as providing descriptive support for the newly added limitations. However, lines 5-7 of page 22 of the specification state the following:

> 'portion of the parent peptide and which retains immunogenicity. It is generally understood in the field of immunochemistry that such peptides must be at least about six residues long in order to be antigenic. Thus any fragment should be at'

There is no mention of the term 'consecutive' in this part of the specification. Since a peptide can also contain a non-linear epitope represented by at least six non-consecutive or discontiguous amino acid residues, it does not appear that the instant specification as originally filed has descriptive support for the now recited 'immunogenic fragment' of narrower scope having at least six 'consecutive' amino acids of SEQ ID NO: 6, as recited. Therefore, the new limitations added to claim 17 are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitations, or to remove the new matter from the claim(s).

20) Claims 12 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 12 and 20 have been amended to delete the Markush recitations of SEQ ID NO: 5 or an immunogenic fragment thereof, SEQ ID NO: 7 or an immunogenic fragment thereof, SEQ ID NO: 8 or an immunogenic fragment thereof, and an immunogenic fragment of SEQ ID NO: 6. Claims 12 and 20, as amended now, include the new limitation: 'composition comprising one or more peptides ..... the peptides comprising the amino acid sequence of SEQ ID NO: 6' [Emphasis added]. However, there appears to be no descriptive support for a therapeutic composition, as now claimed, comprising one or more peptides, the peptides comprising the amino acid sequence of SEQ ID NO: 6. Therefore, the new limitations are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitations, or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Written Description)

21) Claim 15 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that the peptide having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 6 (i.e., a peptide variant) as described in the instant specification does not exist independent of its function. Although the peptide variant claimed in claim 15 is not currently recited to have any function, the specification discloses diagnostic applications, vaccine (prophylactic) and therapeutic intentions for the peptide. The purified peptide variant(s) present in the therapeutic composition of claims 16 and 18 that depend from claim 15 is required to confer 'protective immunity against *S. pneumoniae* infection when administered to a subject'. However, the instant specification fails to teach a single 'variant' having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 6, which concurrently has at least the ability to be *S. pneumoniae*-specific, or the ability to confer 'protective immunity against *S. pneumoniae* infection when administered to a subject'. Diagnostic, prophylactic or therapeutic applications minimally require an ability of the peptide variant to elicit a specific immune response or bind immunospecifically to an antibody. The precise structure or relevant identifying characteristics of each DNA molecule that encodes a 'variant' peptide of SEQ ID NO: 6 having the specific binding ability, specific immunogenicity, or ability to confer protective immunity against *S. pneumoniae* infection in a subject can be determined empirically by actually making DNA molecules that encode the peptide variant, and testing each varied DNA molecule to determine whether it encodes the recited peptide variant having the particularly disclosed specific binding activity, immunogenicity, or ability to confer protective immunity against *S. pneumoniae* infection in a subject. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement that the invention includes a peptide variant having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 6 is insufficient to meet the adequate written description requirement of the claimed invention. The peptide of SEQ ID NO: 6 has specific biologic properties dictated by the structure of the peptide and the corresponding structure of the structural gene sequence, which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the peptide encoded, and the function of the encoded peptide. The function cannot be predicted from the modification of the structure of the gene and in the instant case, the DNA encoding the recited peptide variant. Applicants have not shown that variation or modification of a reference sequence encoding a reference peptide as claimed would automatically predict the production of a peptide variant having the recited or intended functional activity, i.e., ability to bind, ability to be *Streptococcus pneumoniae*-specific, or ability to confer protective immunity against *S. pneumoniae* infection when administered to a subject. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of peptide variants of SEQ ID NO: 6 as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the exception of a pneumococcal peptide consisting of SEQ ID NO: 6 which binds specifically to a PsaA-specific monoclonal antibody, a skilled artisan cannot envision the detailed chemical structure of the peptide variant species encompassed by the recited or claimed molecule. Because the genus is highly variable and since the disclosure and claims fail to describe the common attributes or characteristics that identify members of the genus, a peptide molecule 'consisting' of SEQ ID NO: 6 is insufficient to describe the genus of peptide molecules comprising SEQ ID NO: 6 and variants thereof comprising amino acid sequences at least 90% identical to SEQ ID NO: 6. In claim 15, Applicants have not described a function which is shared by a peptide molecule of SEQ ID NO: 6 and by peptide variant species comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 6. Therefore, one of skill in the art would reasonably conclude that the instant disclosure fails to provide for a representative number of species to describe the genus. The single described species of a peptide consisting of the amino acid sequence of SEQ ID NO: 6 is not representative of the entire genus which includes significant number of peptide variants. Clearly, Applicants were not in possession of the claimed genus. The description of SEQ ID NO: 6 is

insufficient to describe the necessary common attributes of the peptide variants claimed, i.e., 'variants' of SEQ ID NO: 6 comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 6. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 makes clear that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*'. See *Vas-Cath* at page 1117. The specification does not 'clearly allow persons of ordinary skill in the art to recognize that [she or he] invented what is claimed'. See *Vas-Cath* at page 1116. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that its is a part of the invention and a reference to a potential method of isolating it. Actual reduction to practice is required when conception is otherwise incomplete. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.*

Rejection under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

22) Claims 12, 15, 16, 18 and 20 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for an immunogenic purified peptide comprising the amino acid sequence of SEQ ID NO: 6 which binds to a monoclonal antibody immunospecific to an isolated 37 kDa *S. pneumoniae* PsaA protein, and a composition comprising the same in an adjuvant or an immunostimulatory carrier, does not reasonably provide enablement for a purified peptide comprising an amino acid sequence which is 'at least 90% identical' to the peptide of SEQ ID NO: 6, or a therapeutic composition comprising the same, wherein the composition 'confers protective immunity against *S. pneumoniae* infection when administered to a subject' as recited in claims 16 and 18. The specification does not also reasonably provide enablement for a 'therapeutic' composition comprising one or more peptides comprising SEQ ID NO: 6, wherein the therapeutic composition confers protective immunity against *S. pneumoniae* infection when administered to a subject' as claimed in claims 12 and 20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Claims 16 and 18 are drawn to a therapeutic composition comprising a purified peptide that is 'at least 90% identical to the peptide of SEQ ID NO: 6'. The composition of claims 16 and 18 is *required* to confer 'protective immunity against *S. pneumoniae* infection when administered to a subject. Claims 16 and 18 depend from claim 15, the peptide product of which is unassociated with a function. Thus, the nature of the invention is in the area of less than 100% identical microbial peptides having the ability to confer 'protective immunity against *S. pneumoniae* infection when administered to a subject'. The phrase 'at least 90%identical to the peptide of SEQ ID NO: 6' indicates that the recited peptide is a peptide 'variant' having amino acid substitution(s), insertion(s) or deletion(s). Although the relative skill of those in the art of peptide variation is high, the state of the art on peptide, protein or polypeptide variation or substitution suggests a high degree of functional unpredictability as described below. Whenever the art documents unpredictability, those of skill in the art would look into Applicants' specification for specific disclosure and guidance in order to make and use the novel invention claimed, which in the instant case lacking as explained below.

The therapeutic composition comprising the peptide having 'at least 90%' identity to the peptide of SEQ ID NO: 6 (i.e., peptide variant) as claimed in the dependent claims 16 and 18 is *required* to confer protective immunity against *S. pneumoniae* infection when administered to a subject. The peptide variant claimed in the base claim 15 is *required* to be at least *S. pneumoniae*-specific, although not recited as such, since the product claimed in the dependent claims 16 and 18 cannot be expected to confer protective immunity against *S. pneumoniae* infection in a subject, if the peptide variant of claim 15 is not *S. pneumoniae*-specific. In the instant case, 'protective

immunity' is defined as being equivalent to the generation of neutralizing antibodies that bind to the immunogenic component of the pathogen in such a way that proliferative infection by the pathogen is inhibited or abrogated such that the subject remains essentially free of symptomatic disease (see paragraph bridging pages 4 and 5 of the specification). A review of the specification indicates that there are no working examples showing that a peptide variant having at least 90% identity, i.e., as much as 10% non-identity to SEQ ID NO: 6, was indeed produced and administered to a human or non-human subject that is susceptible to *S. pneumoniae* infection in whom it conferred protective immunity against *S. pneumoniae* infection by inducing neutralizing antibodies that inhibited proliferative infection by *S. pneumoniae*. Thus, the breadth of the claims encompasses a therapeutic composition comprising peptide variants of SEQ ID NO: 6 that are not enabled as 'protective' immunogens. Adding to the lack of working examples in the instant specification are other *Wands* factors such as the breadth of the claims, the lack of disclosure and specific guidance and the unpredictability factor. The unpredictability factor cannot be dismissed in the face of state of the art on peptide variation, but must be included in *Wands* analysis.

Although a microbial polypeptide or protein is expected in the art to generally induce specific antibodies, the ability of peptide variants having at least 90% sequence identity, i.e., as much as 10% non-identity to the peptide of SEQ ID NO: 6, to confer protective immunity against a disease due to any serotype of *S. pneumoniae*, is not predictable, absent a concrete showing. The instant specification fails to teach how to produce a peptide variant having at least 90% sequence identity to the peptide of SEQ ID NO: 6 such that it can be included in a therapeutic composition that is *required* to confer protective immunity against any serotype of *S. pneumoniae* infection in a human or non-human subject. The specification provides no specific guidance as to which specific amino acid(s) must be retained and which may be varied within the peptide of SEQ ID NO: 6 without causing any detrimental effect to the peptide that is meant to be included in a therapeutic composition which is required to induce a protective immune response in a subject against *S. pneumoniae* infection. There is no guidance in the instant specification with regard to which amino acid variations, i.e., insertions, deletions, additions and substitutions, in the peptide would result in a peptide variant of the recited percent identity that would retain the three-dimensional structure and the functional integrity or biological/immunogenic and protective competence of the native protein

or peptide, without rendering it non-functional. Except for a full length 37-kDa protein of *S. pneumoniae* that confers protective immunity against challenge with a wild-type *S. pneumoniae,* there appears to be no evidence within the instant specification, as originally filed, showing that the unmodified native peptide of SEQ ID NO: 6, or a variant thereof having 90% sequence identity to SEQ ID NO: 6, is capable of remaining *S. pneumoniae*-specific, let alone be capable of conferring protective immunity against infection by any serotype of *S. pneumoniae.* There is not even a showing that the unmodified (native) 15 amino acid-long peptide of SEQ ID NO: 6, let alone its variant that having at least 90% sequence identity, does indeed comprise a protective epitope and does confer protective immunity against *S. pneumoniae* infection in a human or non-human subject. In other words, the reference peptide of SEQ ID NO: 6 itself is not established to have the ability to confer protective immunity against *S. pneumoniae* infection in a subject. A review of the specification suggests that the 'Results' section on page 31 and Example 4 of the specification describe the protective ability of the full length 37-kDa protein of *S. pneumoniae.* Table 4 shows that the peptide of SEQ ID NO: 6 reacts with 1B6 monoclonal antibody. This binding to 1B6 monoclonal antibody only establishes that the peptide of SEQ ID NO: 6 comprises an antigenic epitope, as opposed to a protective epitope. Example 14 shows that the peptide of SEQ ID NO: 6, when conjugated to KLH and mixed with an adjuvant, is immunogenic in mice and nothing more. The protection experiments described in Examples 4 and 5 are **limited** to a showing that the whole 37-kDa protein of *S. pneumoniae* confers protection in mice against challenge with a wild-type *S. pneumoniae.* There is simply no showing that the peptide of SEQ ID NO: 6, or a variant thereof having at least 10% dissimilarity to SEQ ID NO: 6, is protective against *S. pneumoniae* infection in any subject. The *S. pneumoniae*-specificity of the peptide of SEQ ID NO: 6, or a variant of the peptide of SEQ ID NO: 6 as recited, is neither established, nor predictable. This is important because the art reflects unpredictability as to which amino acids in a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional or biological properties of that specific protein. While it is known in the art that variation in one or more amino acids is possible in a given protein, the exact position within its amino acid sequence where replacements or variations can be made, with a reasonable expectation of success of retaining the protein's functional integrity, is not certain. A random replacement affecting the epitopic amino acid positions that are critical,

for example, to the three-dimensional conformational structure and specific binding property of the protein, would result in a polypeptide that may be non-functional, i.e., non-immunogenic or not optimally immunogenic or protective as a therapeutic composition or a vaccine candidate, because such positions tolerate no or little modification(s). As set forth previously, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986, already of record) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively **unrecognizable** by any of the antibodies in the polyclonal pool. [Emphasis added]

Thus, the art reflects that variations in critical residues at specific positions in an amino acid sequence could result in a polypeptide which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. If the antibody induced by a peptide variant does not recognize or immunospecifically bind to the native microbial polypeptide on *S. pneumoniae*, such a peptide or a composition comprising the same would not be 'therapeutic' or 'protective' against *S. pneumoniae* infection. It is noted that Applicants have dismissed the cited teachings of Houghten *et al.* and have failed to advance any arguments while continuing to allege that the Office has provided no factual basis.

In the instant case, one of the purposes of the instant invention is to produce a peptide of SEQ ID NO: 6, or a 90% identical variant of the peptide of SEQ ID NO: 6 of *S. pneumoniae* in its biologically active, immunogenic and/or protective form for inducing a protective immune response against *S. pneumoniae* infection in a subject, human or non-human. The instant disclosure lacks guidance on the precise position(s), nature and extent of amino acid replacements or variations that can be made in the claimed peptide in order to produce a variant with 90% identity to SEQ ID NO: 6, and with regard to whether it would confer protective immunity against *S. pneumoniae* infection in a human or a non-human subject. This is critically important because, contrary to Applicants' assertion, the art reflects sensitivity of proteins or polypeptides to alteration of even a single amino acid residue in its amino acid sequence. It is known in the art that an alteration in a single amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance,

Burgess *et al* (*J. Cell Biol.* 111: 2129-2138, 1990) taught that replacement of a single lysine residue at position 118 of the protein, acidic fibroblast growth factor, by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar *et al* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) provided similar teachings by showing that replacement of aspartic acid with alanine or asparagine at position 47 of the protein, transforming growth factor alpha, did not affect its biological activity, while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. In light of these art-established findings, it is unlikely that a peptide molecule having as much as 10% dissimilarity with the native peptide of SEQ ID NO: 6 as recited, would have its primary, secondary or tertiary structure unchanged and would have the therapeutic and immunoprophylactic activities and *S. pneumoniae*-specificity retained. The effects of such dissimilarity upon the polypeptide structure and function are unpredictable. Bowie *et al.* (*Science* 247: 1306-1310, 1990) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further taught that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). Bowie *et al* also taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function(s) is limited. Certain positions in the polypeptide sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). The state of the art reflects functional unpredictability even with regard to conservative amino acid substitutions. For instance, Lazar *et al.* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) demonstrated that a substitution of Leu with a conservative amino acid residue, such as, Ile or His, in the transforming growth factor (TGF) alpha led to a mutant protein with dramatically altered biological activities. Lazar *et al.* stated that they 'did not expect that a mutation of Leu to Ile (which have similar sizes and polarities) would cause such a strong effect'. See paragraph bridging left and right columns on page 1251; and third full paragraph on page 1251. Applicants assert that one of skill in the art

would be able to make a single amino acid variation in SEQ ID NO: 6 by routine experimentation. However, Applicants have failed to show that such a single amino acid variation in the peptide of SEQ ID NO: 6 would result in a peptide variant that would retain the functional and biologic integrity (i.e., the protective ability) of the PsaA protein and that can be used for the protective purpose in a therapeutic composition.

McGuinnes *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993 and *Lancet* 337: 514-517, March 1991) have demonstrated the criticality of a single amino acid substitution in a microbial peptide and the adverse influence such a variation has on the immunospecificity of the peptide. McGuinnes' peptide is from a bacterial pathogen which is represented by several distinct serotypes, similar to the instantly recited *S. pneumoniae*. With specific reference to a meningococcal peptide, McGuinnes *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993) teach that '[a] single amino acid change within an epitope, or an amino acid deletion outside an epitope, were both associated with loss of subtype specificity resulting from a change in the predicted conformation at the apex of the loop structure' (see abstract). Similarly, McGuinnes *et al.* (*Lancet* 337: 514-517, March 1991) teach that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 results in 'striking changes in the structural and immunological properties of the class 1 protein' of this isolate (see abstract and page 514). Thus, while the art demonstrates that even a single amino acid substitution will often dramatically affect the biological activity and immunogenic characteristics of a peptide, with as much as 10% dissimilarity to the peptide of SEQ ID NO: 6, the therapeutic and *S. pneumoniae*-specific protective activities of the recited peptide variant could not be predicted, based solely on the sequence identity, nor would it be expected to be the same as that of the native 37 kDa PsaA protein. One simply cannot predict what effects a given deletion, insertion or modification in the amino acid sequence would cause, and therefore such modified molecules are not enabled as Applicants' invention. In the instant application, the purified native peptide of SEQ ID NO: 6 itself is not shown to confer protective immunity against *S. pneumoniae* infection in any subject. If one produced peptide variants of SEQ ID NO. 6 as recited, there is no predictability or certainty that amino acid substitutions at any position would yield a peptide variant that retains the biological function and/or the *S. pneumoniae*-specificity of the pneumococcal 37 kDa PsaA protein. The state

of the art has established that the ability of a random peptide of a microbial protein to elicit a species-specific or genus-specific protective immune response in a subject is not predictable. For instance, specifically with regard to a streptococcal Spa peptide, Dale *et al.* (*J. Clin. Investigation* 103: 1261-1268, May 1999) established that a 23 amino acid-long fragment, S-Spa18(1-23)C, having no variation or amino acid substitution, is incapable of providing protection against heterologous Group A streptococci and therefore, against the Group A streptococcal genus. Similarly, Dale (US 6,716,433) showed that the Spa fragment, S-Spa18(1-23)C, 'did not opsonize' type 3 or type 28 group A streptococci, thus indicating the absence of cross-opsonic epitopes in the fragment (see Example 6). This is *prima facie* evidence that one cannot predict a 15 contiguous amino acid-long fragment from PsaA protein, having the amino acid sequence of SEQ ID NO: 6, or a peptide variant thereof having 90% identity to SEQ ID NO: 6, to elicit protective immune response against one or more serotypes of *S. pneumoniae*, or against any specific serotype of *S. pneumoniae*.

Applicants have not enabled the full scope of the invention as claimed for those peptide variant molecules, which are altered or varied. The enabling disclosure in the instant specification is limited to a purified peptide of SEQ ID NO: 6 and a composition comprising the same. The altered peptide of at least 90% identity would vary in an unknown or unpredictable manner from the disclosed native peptide sequence. The lack of disclosure combined with the art-recognized unpredictability would require one of skill in the art to engage in considerable undue experimentation. For these reasons, making and using of the instantly claimed peptide or its variant having the recited/intended function(s) or use, is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the lack of working examples, the art-demonstrated functional unpredictability as reflected in the state of the art, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Applicants are reminded that the courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to

constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).* Moreover, the specification must have been enabling at the time the invention was made (see *In re Wright, 27 USPQ2d 1510*). A claim must be enabled over its whole breadth. In this respect, if there are doubts, substantiated by verifiable facts, there is lack of sufficient enablement.

The state of the art has established that the ability of a random peptide of a microbial protein to elicit a species-specific or genus-specific protective immune response in a subject is not predictable. For instance, specifically with regard to a streptococcal Spa peptide, Dale *et al.* (*J. Clin. Investigation* 103: 1261-1268, May 1999) established that a 23 amino acid-long fragment, S-Spa18(1-23)C, having no variation or amino acid substitution, is incapable of providing protection against heterologous Group A streptococci and therefore, against the Group A streptococcal genus. Similarly, Dale (US 6,716,433) showed that the Spa fragment, S-Spa18(1-23)C, 'did not opsonize' type 3 or type 28 group A streptococci, thus indicating the absence of cross-opsonic epitopes in the fragment (see Example 6). This is *prima facie* evidence that one cannot predict a 15 contiguous amino acid-long fragment from PsaA protein, having the amino acid sequence of SEQ ID NO: 6, or a peptide variant thereof having 90% identity to SEQ ID NO: 6, to elicit protective immune response against one or more serotypes of *S. pneumoniae*, or against any specific serotype of *S. pneumoniae*.

In sum, the instant disclosure lacks guidance on the precise position(s), nature and extent of amino acid replacements, deletions or variations that can be made in the polypeptide of SEQ ID NO: 6 in order to produce a functional 90% identical peptide variant thereof, and with regard to whether it would serve as an effective immunogen capable of conferring immunity against *S. pneumoniae* disease. Predictability or unpredictability is one of the *Wands* factors for enablement. There is no evidence that the claimed peptide variants were indeed made and tested for their ability to serve as effective protective immunogens suitable for use in a therapeutic composition. Since the state of the art reflects that the claimed invention is in an unpredictable art, absent a concrete showing that the claimed peptide variants, are effective as specific protective immunogens against any serotype of *S. pneumoniae* and eliminate or reduce morbidity and/or mortality due to infections by *S. pneumoniae*, the claims are considered as being non-enabled. Clearly, the specification lacks adequate guidance and disclosure that would limit the experimentation from being undue. Making

and using of the instantly claimed peptide variants having the recited function(s) is well outside the realm of routine experimentation. Given the art-recognized unpredictability associated with the structure-function relationship of a varied peptide, one of skill in the art would look into Applicants' specification for specific teaching and guidance, which in the instant case is lacking. Due to the lack of specific guidance and disclosure as to the precise structure of the peptide variants that remain functional and *S. pneumoniae*-specific; the lack of demonstration of their specific protective ability; the lack of working examples enabling the full scope of the claims; the art-recognized unpredictability factor associated with the retention of functions of a peptide following one or more variations; the breadth of the claims; and the quantity of experimentation necessary, undue experimentation would have been required to practice the invention as claimed. *Ex parte Foreman*, 230 USPO 546, 547 (*Bd. Pat. Appeals. and Inter.* 1986). The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001)*. Moreover, the specification must have been enabling at the time the invention was made. See *In re Wright, 27 USPQ2d 1510.* A claim must be enabled over its whole breadth. In this respect, if there are doubts, substantiated by verifiable facts, there is lack of sufficient enablement.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

23) Claims 2, 6, 12, 15, 16, 18, 20 and 23 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 2 is vague, indefinite, incomplete and confusing in the recitation: 'monoclonal antibody, 1B6E12H9, deposited with the ATCC under accession number _____'. The claim lacks the accession number. Furthermore, it is unclear whether what is deposited at the ATCC is the recited monoclonal antibody itself, or the hybridoma cell line that produces the recited monoclonal antibody.

(b) Claim 6 is vague and indefinite in the limitation: 'peptide described in claim 2'. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation with --peptide claimed in claim 2--.

(c) Analogous criticism applies to claims 16 and 18 with regard to the claim language: 'described in claim ...'.

(d) Claim 6 is vague, indefinite, confusing and/or incorrect in the limitation: 'immunogenic against *S. pneumoniae* comprising the amino acid sequence of SEQ ID NO: 6'. The claim language makes no sense.

(e) Claims 16 and 18 have improper antecedent basis in the limitation: 'the peptides described in claim 15', because claim 15 does not recite any 'peptides' [Emphasis added].

(f) Claims 12 and 20 are indefinite and confusing in the limitation: 'the peptides comprising the amino acid sequence of SEQ ID NO: 6', because it is unclear how the amino acid sequence of SEQ ID NO: 6 can represent more than one peptide. It is further unclear how this limitation differs in scope from the limitation in claims 15 and 6: 'the peptide of SEQ ID NO: 6'.

(g) Claim 23 lacks a preceding article before the limitation: 'monoclonal antibody'. It is suggested that Applicants replace the limitation with --a monoclonal antibody--.

(h) Claims 6, 16 and 18, which depend from claim 2 or 15, are also rejected as being indefinite, because of the indefiniteness or vagueness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

24) Claims 6, 12, 15, 16, 18, 20 and 23 are rejected under 35 U.S.C § 102(e) as being anticipated by Sampson *et al.* (US 6,217,884, already of record) ('884) as evidenced by Jarecki-Black (US 6,368,603).

It is noted that the purified peptide claimed in claim 15 has no function and is not required to show any immunospecific antibody binding. Unlike the peptide claimed in claims 2 and 6, the 'peptide' claimed or recited in claims 12, 20 and 21 is not limited to a peptide immunospecifically binding with the 1B6E12H9 monoclonal antibody, but encompasses peptides immunospecifically binding to any monoclonal antibody other than the 1B6E12H9 monoclonal antibody.

Sampson *et al.* ('884) disclosed a fragment (i.e., peptide) of a 37 kDa protein of *S. pneumoniae* which is used as a vaccine component as well as a reagent for identifying host

antibodies raised against *S. pneumoniae* during infection. The specific monoclonal antibody used is **1B6E12H9**; 1E7A3D7C2; 1B6E12H9; 3C4D5C7; 4E9G9C3; 4H5C10F3; and 6F6F9C8; or 8G12G11B10 (see abstract; and column 7, lines 40-46; all of columns 11 and 12 including the paragraph bridging columns 11 and 12; and column 13, lines 1-46). The monoclonal antibody was obtained by immunizing an animal with *S. pneumoniae* PsaA (see lines 18-20 in column 12). The third paragraph under the section '37 kDa protein' in the last paragraph of column 7 of the '884 patent discloses that Sampson's ('884) PsaA fragment is purified. The composition comprises a unique fragment (i.e., a peptide) of the 37-kDa pneumococcal surface adhesion protein (i.e., PsaA) for use in inoculating a host such that the polypeptide fragment generates an active immune response in the host which protects the host from infection (see column 13, seventh full paragraph). Sampson *et al.* ('884) disclosed PsaA fragments, i.e., peptides, encoded by a unique at least 10 nucleotides of SEQ ID NO: 1, and larger peptides. The phrase 'at least 10 nucleotides of SEQ ID NO: 1' encompasses 20 nucleotides, 30 nucleotides, 40 nucleotides, 50 nucleotides, 60 nucleotides etc. As Applicants have acknowledged previously, Sampson's monoclonal antibodies bind to such a polypeptide fragment or peptide. One of skill in the art would expect such a peptide from the 37 kDa protein to be immunogenic. One of skill in the art would reasonably expect at least one of Sampson's PsaA fragments to bind immunospecifically to at least one of the monoclonal antibodies identified above, including the monoclonal antibody specifically recited in claim 2, **1B6E12H9**. The composition comprises a pharmaceutically acceptable carrier and adjuvants (see column 14, lines 1-24). Synthetic peptides disclosed include shorter and larger peptides (see last paragraph in column 10) or partial polypeptides (see first full paragraph). The immunoreactive fragment of the 37 kDa pneumococcal surface adhesin protein is at least about 6 consecutive amino acids (i.e., inclusive of 10-15, 12-22 or 15 amino acid residues in length) having the ability to evoke an immune response (see lines 52-59 in column 11). The fragments are produced by selected modifications, provided the immunogenicity of the peptide is not significantly impaired compared to the 37 kDa pneumococcal surface adhesin protein (see paragraph bridging columns 11). Since it is well known in the art that a monoclonal antibody has a single specificity, the purified prior art PsaA peptide has to necessarily have the structure of SEQ ID NO: 6 and has to necessarily bind immunospecifically to Sampson's mAb 1B6E12H9. Therefore, the PsaA peptide and the

composition thereof disclosed by Sampson *et al.* anticipate the instantly claimed peptide and the composition comprising the same.

It is very well known in the art that a monoclonal antibody has a single specificity and therefore it binds immunospecifically with a single antigenic determinant. For example, see lines 15-17 of column 12 of Jarecki-Black. Therefore, Sampson's ('884) fragments or peptides derived from the *S. pneumoniae* PsaA protein and immunoreactive with the 1B6E12H9 monoclonal antibody do contain and has to contain the instantly claimed or recited peptide.

Claims 6, 12, 15, 16, 18, 20 and 23 are anticipated by Sampson *et al.* ('884).

25) Claims 2, 6 and 23 are rejected under 35 U.S.C § 102(b) as being anticipated by Nuijens *et al.* (WO 9117258, already of record) as evidenced by Srivastava *et al.* (*Hybridoma* 19: 23-31, 2000, already of record) and Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual.* Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, already of record).

It is noted that the peptide claimed in claims 2 and 23, and the 'immunogenic fragment' recited in claim 6, are not structurally identified.

The transitional limitation 'comprising' similar to the limitations, such as, 'having', 'including', 'containing', or 'characterized by' represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts').

Nuijens *et al.* disclosed a composition comprising a purified peptide having the sequence, SYQHDL, which shows 100% sequence identity with the identical six amino acid-long sequence SYQHDL comprised within the SEQ ID NO: 6 recited in claims 6 and 23. The peptide is conjugated to a suitable carrier to enhance elicitation of an antibody response. See the sequence alignment provided below; claims 15 and 17; and Example II of Nuijens *et al.*

```
RESULT 6
AAR14929
ID   AAR14929 standard; Protein; 12 AA.
XX
AC   AAR14929;
XX
DT   13-FEB-1992  (first entry)
XX
DE   OT-2 antibody binding peptide (2).
XX
KW   Monoclonal antibody; antigen; immunogen; Factor XII; epitope.
XX
OS   Synthetic.
XX
PN   WO9117258-A.
XX
PD   14-NOV-1991.
XX
PF   01-MAY-1991;   91WO-US02990.
XX
PR   10-MAY-1990;   90US-0521820.
XX
PA   (CETU ) CETUS CORP.
XX
PI   Nuijens JH,  Huijbregts CCM,  Hack CE;
XX
DR   WPI; 1991-353779/48.
XX
PT   Treatment of sepsis using inhibitor of factor XII activation -
PT   comprises use of new OT-2 antibody
XX
PS   Claim 15,17; Page 24; 32pp; English.
XX
CC   Based on the known amino acid sequence of Factor XII, peptides
CC   corresp. to neutralising epitopes of the mol. are synthesised and
CC   used as immunogens to produce antibody.  The pref. peptides are
CC   represented in AAR14928-30.  Amino acid Asp in this sequence =
CC   residue 442.
XX
SQ   Sequence   12 AA;

  Query Match          40.0%;  Score 6;  DB 12;  Length 12;
  Best Local Similarity   100.0%;  Pred. No. 4.1;
  Matches    6;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       2 SYQHDL 7
           ||||||
Db       5 SYQHDL 10
```

SEQ ID NO: 6

Although Nuijens *et al.* are silent about the binding of the peptide sequence SYQHDL to a monoclonal antibody, or the 1B6E12H9 monoclonal antibody as recited, the prior art peptide sequence is viewed as the same as Applicants' peptide claimed in claims 2 and 23, or the at least six consecutive amino acids-containing immunogenic fragment of SEQ ID NO: 6 as recited in claim 6. The Office's position that Nuijens' peptide is the same as the Applicants' peptide as claimed in claims 2 and 23, or the at least six consecutive amino acids-containing immunogenic fragment of SEQ ID NO: 6 as recited in claim 6, is based upon the fact that every structural characteristic overlapping in Nuijens' and Applicants' disclosure are the same. In spite of the fact that Nuijens *et al.* are silent about the binding limitations, since the prior art peptide sequence SYQHDL is structurally the same as the instantly claimed sequence SYQHDL from SEQ ID NO: 6, the prior art peptide sequence is expected to bind immunospecifically to a generic monoclonal antibody that binds to SEQ ID NO: 6, or the specific 1B6E129 monoclonal antibody, which was inaccessible to

recited by Applicants is viewed as an inherent property inseparable from the peptide sequence of Nuijens *et al.* Due to the 100% sequence identity between Nuijens' peptide sequence SYQHDL and Applicants' peptide, or immunogenic fragment of SEQ ID NO: 6, SYQHDL, the peptide sequence of the prior art is expected to bind immunospecifically to the monoclonal antibody as recited, because both the Applicants and the art recognize that the smallest peptides which elicit antibodies that bind to the original full length protein are 6 amino acids in length. See the first sentence under 'Size of the Peptide' on page 76 of Harlow *et al.* That the prior art SYQHDL peptide sequence does in fact form an epitope for the PsaA-specific monoclonal antibody, 1B6E12H9 (also known as 1B6), is also inherent from the teachings of the prior art in light of what is well known in the art. For instance, see last five lines in the right column of page 24; Table 1; and the top most rectangular box in Figure 1 of Srivastava *et al.* Thus, the SYQHDL epitope-containing peptide existed at the time of the invention as taught by Nuijens *et al.* at Example II, and claims 15 and 17.

The teachings of Nuijens *et al.* anticipate the instant claims. Harlow *et al.* or Srivastava *et al* is **not** used as a secondary reference in combination with Nuijens *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Nuijens *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Where the only difference between the claimed product and the prior art product is recited in the functional language, i.e., by what it does rather than what it is, it is incumbent upon Applicants, when challenged by the USPTO, to demonstrate that the prior art product does not actually possess those characteristics. Applicants have not shown that the underlying structure of the prior art peptide sequence, SYQHDL, differs from that of the instantly recited peptide sequence, or the at least six amino acids-containing immunogenic fragment of SEQ ID NO: 6. The mere functional limitation does not impart a specific structure that distinguishes the prior art peptide sequence SYQHDL from the instantly claimed or recited peptide or the immunogenic fragment of SEQ ID NO: 6.

Claims 2, 6 and 23 are anticipated by Nuijens *et al.*

Relevant Prior Art

26) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Sampson *et al.* (US 6,773,880) disclosed unique fragments of the 37 kDa polypeptide of *S. pneumoniae* and the monoclonal antibody, 1B6E12H9. See sections 'Antibodies' and 'Vaccines'.

Remarks

27) Claims 2, 6, 12, 15, 16, 18, 20 and 23 stand rejected.

28) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (703) 872-9306.

29) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

30) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

April, 05

S. DEVI, PH.D.
PRIMARY EXAMINER